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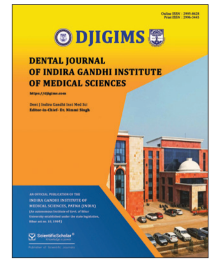

Review Article

Gene Therapy in Orofacial Pain – An Overview

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Received: 01 February 2024
Accepted: 13 February 2024
EPub Ahead of Print: 01 April 2024
Published: 06 April 2024

DOI
10.25259/DJIGIMS_7_2024

Quick Response Code

ABSTRACT

Disorders involving the jaw, mouth, face, head, and neck are diagnosed, managed, and treated under the dental specialty known as orofacial pain (OFP). As the pathophysiology of OFPs is complex, evidence-based knowledge is essential for treating these illnesses effectively. Since OFP affects the affected individuals' quality of life, it is crucial to treat patients with success. As a result of the inter-patient differences, treating OFP remains difficult even with the available therapy options. Gene therapy exhibits promising potential in bridging the gap between medicine and dentistry applications. Gene therapy's dynamic treatment modalities have been developing quickly. Redesigning conventional methods to be more all-encompassing and preventive may eliminate the need for medication and surgery. Genes are sequences of complementary bases that carry the instructions needed to make proteins. One of the most accessible areas for the therapeutic application of gene therapy for various oral tissues is the oral cavity.

Keywords: Orofacial pain, Gene therapy, Recent advances, Conventional approaches

INTRODUCTION

Any discomfort experienced in the mouth, jaws, or face is referred to as orofacial pain (OFP). Various people react to the same noxious stimuli differently and experience pain at various intensities.[1] Twenty-seven percent of the 1,254 people surveyed in 1986 who completed the Nuprin pain report, reported experiencing dental pain, while 73% reported having headaches in the preceding year. Twelve percent of patients who complained of headaches saw a dentist to find out what was the cause of the pain. According to his report, head and neck pain management is a very real task.[2] Professional interest in OFP disorders has grown in the past several years. A brand-new clinical specialty with specialized training in treating OFP syndromes is starting to emerge. It implies that pain is a defense mechanism against harm and that it is mediated by specific brain structures designed for that function.[1]

"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in term of such damage," is how the International Association for Study of Pain (IASP) defines pain.[3] "An unpleasant emotional experience that is typically triggered by a noxious stimulus and transmitted over a specialized neural network to the central nervous system where it is interpreted as such" is another definition that pertains to it.[4]

PAIN DIAGNOSIS

Understanding the issue and making an accurate diagnosis is crucial to addressing OFP. The selection of an appropriate treatment is contingent upon a precise diagnosis. Finding the precise what, where, how, and why of a patient's complaints is the goal of diagnosis. The characteristics of pain complicate the process of diagnosing it.[3]

The process of diagnosing a pain complaint involves the following four main steps:

- Past events;
- Clinical examination;
- Precisely pinpointing the extraction site from where pain originates;
- Determining which pain category best describes the situation being studied.

PROS AND CONS OF GENE THERAPY

Pros

- Novel, promising treatment alternatives: Gene therapy offers hope for novel treatments for illnesses for whom there aren't many other options at the moment. Many illnesses and disorders result in incapacity or early death if therapy is not received. Research indicates that certain illnesses' progression has slowed down or even stopped with gene therapy.
- Early treatment: Gene therapy can stop harm before it starts if it is administered early in a patient's course of treatment. To what extent gene therapy can reverse damage is currently being studied.
- Aims at the root cause of illness: Gene therapy enables the development of medications that can target any one of your body's genes.

Cons

- Not guaranteed: The field of gene therapy research is still in its early stages. These treatments cannot ensure that your illness will be cured or that they will have positive effects. There's a danger the medication won't function or that it will have unanticipated negative effects.
- Difficult procedure: When a foreign material enters your body, it may trigger an immunological reaction that disqualifies you from participating in clinical trials or other therapies in the future.
- Unknown long-term implications: Gene therapy has the potential to have both permanent positive and negative long-term impacts. The effects are uncertain because the science is so fresh.

GENE THERAPY IN OFP

Gene recombination has been aided by research on gene therapy. Enzymes and molecules are in charge of transporting anti-inflammatory cytokines to particular neurotransmitter locations in the central nervous system through transferences with vectors. This regulates impulses and influxes associated with neural excitability that results in hyperalgesia.

Gene therapy appears to have a bright future in terms of bridging the gap between clinical dentistry and medicine. Gene therapy aims to produce functional proteins by substituting defective genes with their appropriate equivalents. Evidence suggests that gene therapy may be used to prevent, lessen, or even cure underlying illnesses such as genetic disorders, viral infections, and autoimmune disorders.[5] In research institutes across the globe, scientists are working to remove diseases at their source. Rather than looking for drugs to treat illnesses, they are trying to change the genes that cause diseases. This is accomplished by the use of gene therapy. With time, new gene-transfer technologies, procedures, strategies, and viewpoints have surfaced. The phrase "gene therapy," which was first coined in the early 1980s to refer to "genetic replacement treatment," has now evolved beyond its original meaning and is now used to refer to any procedure involving the transfer of genes.[6]

In the first two stages of gene therapy, the therapeutic protein is first cleaved and then inserted into the human genome using an attenuated carrier or vector. The targeted human cells are exposed to the modified vector in the second step, which releases the DNA sequence integrated into a chromosome. Once the gene is "switched on" at the proper location, the cells with the new genetic design eventually produce the necessary therapeutic proteins.[5,7,8] The two main stages of gene therapy are somatic and germline gene treatments, respectively.[9] Gene transfer can be accomplished through two different methods, depending on how the vector is delivered: ex vivo gene transfer, which entails injecting the genetically modified vector into cultured tissue cells before the altered tissues are actually transferred into the body, or in vivo gene transfer, which entails injecting the genetically modified vectors directly into the patient.[8,10]

Research is being conducted on the potential of gene therapy to effectively manage chronic pain by lowering the need for drugs that carry a risk of systemic toxicity, opioid addiction, and other negative side effects.[11] Gene therapy is now largely utilized to relieve pain in animal models. It was recently demonstrated that in a mouse model, trigeminal pain was decreased when the human preproenkephalin gene was expressed using a herpes simplex vector.[12] Gene therapy may become more successful in the future in treating pain syndromes such as trigeminal neuralgia and temporomandibular joint disorders because of improved vector gene systems.[13, 14]

RECENT ADVANCES OF GENE THERAPY

Many stimulus-responsive nanocarriers have been designed in order to transfer genes more precisely and efficiently in order to treat diseases that cannot be treated with a single stimulus-responsive gene carrier. Systems employing numerous stimulus responses are able to adapt to a variety of inputs. To give an example, two polymeric micelles with poly(N-isopropylacrylamide) substrates functionalized with sulfonamide were employed to create pH/temperature sympathetic nanocarriers. When activated with a proof-of-concept antiproliferative drug in mildly acidic conditions (pH 6.8), both sulfadimethoxine and sulfamethazine surface-functionalized micelles showed higher intracellular uptake at temperatures well above their lower critical solution temperatures. Both types of microemulsions could be used as a gene delivery or intracellular pH and temperature-responsive medication.[15]

ATYPICAL OROFACIAL PAIN

A significant aspect of dentistry practice is pain management or elimination. Utilizing gene transfer technology presents a potentially innovative method to control particular, localized biochemical processes implicated in the production of pain. For the treatment of intractable and chronic pain, gene transfer may be especially helpful. Numerous investigations utilizing animal models have demonstrated that the transfer of opiate peptide-encoding genes to peripheral and central neurons via viral means can result in antinociceptive effects. Before gene transfer is used therapeutically as a chronic pain management technique, more research is required. The most popular approaches for gene treatment of pain involve using gene transfer rather than medication administration to produce the continuous release of short-lived bioactive peptides in or near the spinal dorsal horn. Chronic pain management techniques have included transducing neurons of the Dorsal Root Ganglia by injection of herpes simplex virus–based vectors into the skin, injecting vector viruses carrying the gene for an endogenous opioid, and intrathecal injection of vectors derived from adenovirus, AAV, or lipid encapsulated plasmids coding interleukin-10. It has also been discovered that direct gene delivery to the temporomandibular joint's articular surface is possible. New approaches to treating persistent TMJ discomfort may arise from this research.[7,16]

POST-ENDODONTIC PAIN

The pharmacokinetics and dynamics of opioids involve multiple genes, which further complicate the relationship between a patient's genetic makeup and how they respond to opioids. It is evident that a range of genetic variations affect how people perceive pain and react to it. Complex elements such as the prescribed opioid, its route of administration, the pain modality, and the possibility of recurrent unpleasant stimuli all affect how analgesics are reacted to.

The Human Genome Project has made it more likely that medications tailored to each patient's needs will be developed. Genetic variations appear to have an impact on the effectiveness and negative effects of medications used to treat pain. A study looked at the roles that environment and genetics play in the variation in pain sensitivity and opioid analgesic response. Results showed that heredity accounts for at least some of the interindividual variation in opioid responsiveness. It has been determined that over 20 genes influence interindividual variability of human pain sensitivity. Even though there are now some contradicting findings, it's intriguing to consider what genetics may entail for endodontists in the future.

For instance, it has been proposed that markers in the Matrix metalloproteinase-2 (MMP2) and matrix metalloproteinase (MMP3) genes may be able to forecast the healing response as well as the host's propensity to develop periapical lesions. Persistent apical periodontitis may be influenced by genetic predisposition in particular genes. It is expected that gaining knowledge about the genetic foundation of endodontic pain perception would improve our ability to treat postoperative pain with medications.[17,18]

CONCLUSION

There have only been a few clinical applications for periodontal disease therapy and no dentine repair clinical research, despite the great interest in this field. The requirements for manufacturing dependable and reproducible products that are examined for safety and effectiveness must be specified by cell-based bioengineering and material sciences. Gene therapy is a subject of extensive research for a range of biomedical and dental applications. Gene therapy is expected to be a highly useful technique for managing oral diseases and enhancing the quality of life for patients with OFP as well as their prognosis. Physicians now feel confident that gene therapy may soon make its way into practical applications due to the encouraging outcomes of recent human clinical investigations. This kind of biological study will be helpful in the future for clinical orthodontics as, like other biomedical fields, it needs to adapt to new advances in biological applications in order to enhance clinical outcomes and treatment efficacy. Research should be directed toward resolving these issues that keep gene therapy from becoming a widely used treatment option. It is expected that this will be able to overcome the difficulties presented by the clinical applications of gene therapy in the near future. As research and technology progress, dentists will assume a new role as "gene therapists," becoming experts in the therapeutic treatment of orofacial discomfort.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent not required as there are no patients in this study

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The author confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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How to cite this article: Pendharkar SS. Gene Therapy in Orofacial Pain - An Overview. Dent J Indira Gandhi Int Med Sci. 2024;3:32–5. doi: 10.25259/DJIGIMS_7_2024